



## King's Research Portal

DOI:

[10.1016/S2215-0366\(15\)00389-2](https://doi.org/10.1016/S2215-0366(15)00389-2)

*Document Version*

Peer reviewed version

[Link to publication record in King's Research Portal](#)

*Citation for published version (APA):*

Charman, T. (2015). The new genetics of autism: A translational opportunity? *The Lancet Psychiatry*, 2(10), 856-857. [https://doi.org/10.1016/S2215-0366\(15\)00389-2](https://doi.org/10.1016/S2215-0366(15)00389-2)

### **Citing this paper**

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

### **General rights**

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

### **Take down policy**

If you believe that this document breaches copyright please contact [librarypure@kcl.ac.uk](mailto:librarypure@kcl.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.

Tony Charman, PhD

Institute of Psychiatry, Psychology & Neuroscience, King's College London,

Department of Psychology

Box PO77, Henry Wellcome Building

De Crespigny Park

Denmark Hill

London SE5 8AF

UK

Email: [tony.charman@kcl.ac.uk](mailto:tony.charman@kcl.ac.uk)

The new genetics of autism: from rare syndromes to translational opportunities

Richards and colleagues<sup>1</sup> have made a useful contribution to our understanding of the prevalence of autism spectrum disorder (ASD) in genetic and metabolic syndromes.

Their meta-analysis demonstrates that the prevalence rates of ASD in these syndromes range from high (11% in individuals with 22q11.2 deletion syndrome) to very high (36% in tuberous sclerosis complex) to exceedingly high (61% in Rett syndrome). This is against a general population prevalence of around 1%. The findings are of clinical relevance and speak to the ‘new genetics’ of ASD that are unveiling clues to the aetiology of the disorder and hold the potential for translational discovery to develop and test new interventions<sup>2</sup>.

Clinically, the high rates of ASD in these syndromes support the revisions to the DSM-5 diagnostic classification system where the ‘clinical specifiers’ that should be noted alongside an ASD diagnosis include ‘known medical or genetic conditions’<sup>3</sup>. The authors highlight that the recognition of an ASD presentation alongside the genetic/metabolic syndrome will have important implications for management, for example in terms of managing repetitive and rigid behaviours or taking account of impairments in social understanding and communicative functioning. One caveat that should be added to the conclusions of the authors is that alongside intellectual disability (ID) – another clinical specifier in DSM-5 – it is also the case that other common neurodevelopmental and neuropsychiatric conditions (e.g. attention deficit hyperactivity disorder (ADHD), anxiety disorders) that are associated both with ASD and with ID may also be common in these individuals with these syndrome with implications for management<sup>4</sup>. As the Richards et al. recognise, there are significant challenges to the measurement and establishment (and treatment) of both ASD and other associated disorders in individuals with significant ID and the field needs to continue to develop clinically useful solutions to such challenges, as they may offer tractable pathways to better management and treatment.

In basic and translational science terms, the possibility of reconciling our understanding of how single gene disruptions affect neurodevelopment both before and after birth – essentially a ‘bottom-up’ approach to revealing mechanisms of aetiology – with ‘top-down’ approaches such as searching for the genetic substrate of ‘idiopathic’ ASD where there is no known genetic anomaly reflects the crossroads at which the science of ASD has arrived. The fact that most genetic and genomic disorders show both variable expression and pleiotropy<sup>5</sup> raises the question of the

extent to which the association the authors describe between genetic/metabolic syndromes and ASD is specific, or whether such syndromes are associated with more general neurodevelopmental disruption that results in behavioural phenotypes that include features of ASD, ADHD and ID.

Recent attempts to establish greater specificity between the behavioural phenotype of ASD – such as IQ and symptom profiles – and specific genetic substrate have proved more challenging than many hoped<sup>6</sup>. Whilst single gene disorders may have high penetrance in terms of being strongly associated with an ASD phenotype in individuals with such mutations – as clearly demonstrated in this article – most genetic risk for the broader population of individuals with ASD resides in common genetic variation<sup>7</sup>. It is also well established that de novo mutations – copy number variations (CNVs) – are also associated with the ASD phenotype<sup>8</sup>. CNVs that result in loss of function may be more strongly associated with ASD in combination with significant ID, whereas in individuals with ASD with higher IQs inherited genetic influences – as evidenced by higher rates of psychiatric disorders in family members – might play a more major role<sup>9</sup>.

A final consideration of the translational potential of better understanding how genetic and metabolic syndromes contribute to the ASD phenotype and commonly associated phenotypes is the possibility that such discoveries will offer therapeutic opportunities at a neural systems level. One area of focus that has been strongly influenced by recent findings from the study of syndromic forms of ASD are the neural pathways involved in synaptic development and functioning<sup>10</sup>. There is accumulating evidence that these pathways might also be involved in the pathogenesis of nonsyndromic

forms of ASD. After promising findings from preclinical studies within model systems and in human neuronal models, pilot trials have begun to test whether a number of compounds may have therapeutic potential in human patients. Promising targets including mGluR5 antagonists in fragile X syndrome, mTOR inhibitors in tuberous sclerosis and insulin-like growth factor in Phelan-McDermid syndrome<sup>11</sup>. If these studies are successful then trials will begin with these compounds in nonsyndromic or ‘idiopathic’ patients with ASD.

Richards and colleagues have provided a state-of-the-art meta-analytic review that reinforces how commonly the ASD and other associated phenotypes are associated with rare genetic and metabolic syndromes. The challenge for clinicians and scientists in the years ahead is to further develop clinical practice and translational science to put this knowledge to good use for these individuals and those who care for them.

Word count: 790

## References

1. Richards C, Jones C, Groves L, Moss J, Oliver C. The prevalence of autism spectrum disorder phenomenology in genetic disorders: a meta-analytic study. *Lancet Psychiatry*, in press.
2. Geschwind DH, State MW. Gene hunting in autism spectrum disorder: on the path to precision medicine. *Lancet Neurology*, in press.
3. Constantino JN, Charman T. Diagnosis of autism spectrum disorder: reconciling the syndrome, its diverse origins, and variation-in-expression. *Lancet Neurology*, in press.
4. Simonoff E, Pickles A, Charman T, et al. Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity and associated factors in a population-derived sample. *J Am Acad Child Adolesc Psychiatry* 2008; **47**: 921-9.

5. Moreno-De-Luca A, Myers SM, Challman TD, Moreno-De-Luca D, Evans DW, Ledbetter DH. Developmental brain dysfunction: revival and expansion of old concepts based on new genetic evidence. *Lancet Neurology* 2013; **12**: 406-14.
6. Chaste P, Klei L, Sanders SJ, et al. A genomewide association study of autism using the Simons Simplex Collection: does reducing phenotypic heterogeneity in autism increase genetic homogeneity? *Biol Psychiatry* 2015; **77**: 775-84.
7. Gaugler T, Klei L, Sanders SJ, et al. Most genetic risk for autism resides with common variation. *Nat Genet* 2014; **46**: 881-5.
8. Consortium AGP, Szatmari P, Patterson AD, et al. Mapping autism risk loci using genetic linkage and chromosome rearrangements. *Nat Genet* 2007; **39**: 319-28.
9. Robinson EB, Samocha KE, Kosmicki JA et al. Autism spectrum disorder severity reflects the average contribution of de novo and familial influences. *PNAS* 2014; **111**: 15161-5
10. De Rubeis S, He X, Goldberg AP. et al. Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature* 2014; **515**: 209-15.
13. Ebrahimi-Fakhari D, Sahin M. Autism and the synapse: emerging mechanisms and mechanism-based therapies. *Curr Opin Neurol* 2015; **28**: 91-102.

## Abbreviations

ADHD – Attention deficit hyperactivity disorder  
ASD – Autism spectrum disorder  
CNV – Copy number variation  
ID – Intellectual disability  
IGF-1 – Insulin-like growth factor-1  
PMS – Phelan-McDermid syndrome